

The non-technical abstract.

Atherosclerotic vascular disease affecting the lower extremities is the most common form of peripheral arterial disease (PAD) and can lead to clinical conditions ranging from intermittent claudication to ulceration and gangrene. PAD is a disabling syndrome affecting over 10 million patients in the United States. Peripheral artery atherosclerosis impairs blood flow to skeletal muscles in the lower limbs. Growth factors, such as vascular endothelial growth factor (VEGF-A), have been shown in animal studies to improve blood flow the lower limbs by promoting the growth of new blood vessels.

Critical limb ischemia (CLI) is the most serious presentation of lower extremity PAD. An estimated 15-20 percent of patients with lower extremity PAD will advance to CLI, resulting in rest pain and tissue loss (ulcers and gangrene) and the risk of limb amputation. Currently, the most widely used method for diagnosing CLI in patients involves measuring the ankle-brachial index (ABI) and clinical symptoms of the patient.

This clinical study tests the safety and feasibility of gene transfer of an agent (EW-A-401) intended to improve blood flow in the skeletal muscle of patients with critical limb ischemia (CLI). The investigational agent is a circle of genetic material (plasmid DNA) that instructs the body to produce a genetically-engineered transcription factor, a protein that regulates expression of genes. This specific transcription factor has been shown in animal studies to increase expression of the VEGF-A gene, and to promote the growth of new blood vessels. The study agent will be delivered by direct injection into leg muscle.

This is a phase 1, dose-escalation, multiple dose study. The primary outcome measure will be safety and toxicity. In addition, we will collect exploratory effectiveness information including blood flow, walking capacity, pain measurements and blood cell changes.